ACUTE TOXICITY SUMMARY

PHOSGENE

(carbon dichloride oxide; carbonyl chloride)

CAS Registry Number: 75-44-5

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**4 µg/m³**
Critical effect(s)	minor damage to the lower airways
Hazard Index target(s)	Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless gas
Molecular formula	$COCl_2$
Molecular weight	98.92
Density	4.05 g/L @ 25°C
Boiling point	8.2°C @ 760 mm Hg
Melting point	-118°C
Vapor pressure	1,215 mm Hg @ 20°C
Explosive limits	upper = unknown lower = unknown
Solubility	slightly soluble in water; soluble in benzene, glacial acetic acid, and most liquid hydrocarbons
Odor threshold	0.9 ppm
Odor description	musty hay, green corn (Ruth, 1986)
Metabolites	spontaneously hydrolyzes to become HCl and CO_2
Conversion factor	1 ppm = 4 mg/m³

III. Major Uses or Sources

Phosgene is highly chemically reactive and is used as an intermediate in carbonylation reactions in the preparation of many organic chemicals. It was formerly used as a potent chemical warfare "choking" agent. It is currently used in the production of aniline dyes. Occasionally, it is used in the manufacture of some insecticides, in the pharmaceutical industry, and in metallurgy (HSDB, 1994). In addition to its industrial uses, phosgene occurs as a breakdown product of chlorinated hydrocarbons such as tetrachloroethylene or carbon tetrachloride in the presence of short wavelength UV radiation (in heliarc welding of aluminum) or in the presence of hot iron and oxygen. Phosgene is also a breakdown product of chloropicrin.

IV. Acute Toxicity to Humans

Much of the data on human exposures to phosgene comes from military experience, often with poorly characterized exposure conditions. Exposure to phosgene can lead to delayed pulmonary edema, cardiorespiratory arrest, and death (AIHA, 1989). The odor is not helpful in emergency situations since the odor threshold (0.9 ppm) is well above levels that may result in other toxic effects (Amoore and Hautala, 1983).

No evidence exists for a systemic action of inhaled phosgene; the vasculature of the lower respiratory tract appears to be the critical target. After initial exposure, irritation of the lower respiratory tract mucous membranes occurs due to acylation of biological macromolecules. This is followed by a severe reflex vasoconstriction in the lung 2-24 hours later (Arena and Drew, 1986). Hypovolemia with ensuing cardiac arrest may result from massive pulmonary edema. Because of its low water solubility, irritation to the eyes and upper respiratory tract iscomparatively minor compared to the effects on the lower airways. The lowest concentration reported to cause throat irritation is 3 ppm (12 mg/m³) (Henderson and Haggard, 1943). Eye irritation occurs at 4 ppm (16 mg/m³), and 4.8 ppm causes cough (HSDB).

Inhalation of 50 ppm (200 mg/m³) may be rapidly fatal (HSDB, 1994). Phosgene acylates biological molecules easily, thus altering biological membrane integrity and protein structure. Hours after initial exposure, phosgene is hydrolyzed to HCl and CO_2; the former may account for increased irritation to mucosal surfaces.

Predisposing Conditions for Phosgene Toxicity

Medical: Individuals with underlying cardiopulmonary disease may be particularly susceptible to phosgene-induced pulmonary edema.

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

An LC_{50} of 5.1 ppm (20.4 mg/m³) for 30 minutes is reported in mice, and an LC_{50} of 60-70 ppm (240-280 mg/m³) for 15 minutes is reported in dogs (HSDB, 1994).

Exposure of rats to 1 ppm for 4 hours caused excess fluid and fibrin to occur in alveolar spaces immediately following exposure (Currie *et al*., 1985). Pulmonary edema was also observed in guinea pigs exposed to 0.9 ppm phosgene for 5 hours (Cameron *et al*., 1942). Exposure to phosgene at 0.2 ppm for 4 hours caused pulmonary edema in rats, mice, and hamsters, while guinea pigs and rabbits showed similar signs at 0.5 ppm and above (Hatch *et al*., 1986). Exposure of rats to 5 ppm for 10 minutes resulted in pulmonary edema, while exposure to 0.15 ppm for 5.5 hours resulted in increased protein in pulmonary lavage fluid (Diller *et al*., 1985).

Diller and colleagues (1985) exposed rats to various concentrations of phosgene from 0.1 to 5 ppm for time periods of 10 to 500 minutes. Rats exposed to 0.1 ppm phosgene for 4 hours showed histological changes in the lung, whereas no effects were seen after exposure for 1 hour. The histologic changes included highly vacuolated "foamy cells" in the air compartment from the terminal bronchioles to the alveolar ducts and broadening alveolar septae due to cellular elements in the septae and to edematous changes in the interstitia. When compared to measurements of bronchoalveolar lavage fluid protein content, the histological changes were more sensitive indicators of cellular damage due to phosgene. These histological changes indicate oxidative damage to the alveolar region of the lung. Continued damage may result in permeability changes in the pulmonary vascular endothelium, a precursor to pulmonary edema (Pritchard, 1982).

Pulmonary natural killer cell activity was suppressed in rats exposed to 0.5 or 1.0 ppm phosgene for 4 hours (Burleson and Keyes, 1989). Exposure to 0.1 ppm had no significant effect.

Male Sprague-Dawley rats inhaled 0, 0.125, 0.25, 0.5, or 1.0 ppm phosgene for 4 hours (Currie *et al*., 1987a). Rats exposed to 0.5 ppm or greater had significantly increased lung weight (wet and dry). Lavage fluid protein was increased at 0.25 ppm and greater. No effects were noted at 0.125 ppm.

Intracellular ATP levels in rats were diminished and non-protein sulfhydryl groups and associated antioxidant enzymes were increased in lung tissue following acute phosgene exposure (Currie *et al*., 1985; Currie *et al*., 1987b; Jaskot *et al*., 1991).

Female CD-1 mice inhaled 0.1, 0.15, 0.25, or 0.5 ppm phosgene for 4 hours (Illing *et al*., 1988). No changes in body weight, liver weight, or cytochrome P450 levels were noted at any concentration. Exposures to 0.15 ppm or greater significantly increased phenobarbitol-induced sleeping time.

Winternitz et al. (1920) describe the pathology associated with phosgene exposure in animals. Pathological evaluation of dogs exposed for 30 minutes to 44 to 120 ppm (176 to 480 mg/m^3) revealed acute emphysema and atelectasis, mottled lung appearance, fluid filled trachea, edematous larynx, and necrosis of the bronchioles. In other species, phosgene exposure was associated with severe lung edema and inflammatory changes which begin tin the bronchioles and extend into the alveoli. For the rat and monkey a concentration of 80 mg/m^3 was lethal at 30 minutes (no sample size reported).

VI. Reproductive or Developmental Toxicity

No evidence exists to suggest that maternal phosgene exposure directly affects reproduction or fetal development.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 4 μg/m³

Study	Diller *et al*., 1985
Study population	14 rats
Exposure method	inhalation (for 10 to 500 minutes)
Critical effects	histologic changes in the lungs
LOAEL	0.1 ppm for 4 hours
NOAEL	0.1 ppm (0.4 mg/m³) for 1 hour
Exposure duration	1 hour
Extrapolated 1 hour concentration	0.1 ppm
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference Exposure Level	1 ppb (4 μg/m³)

The 0.1 ppm 1-hour NOAEL and 4-hour LOAEL is generally consistent with the findings of a number of other studies. Burleson and Keyes (1989) observed a 4-hour rat NOAEL of 0.1 ppm for suppression of pulmonary natural killer cell activity. Jaskot *et al*. (1991) reported a 4 hour rat LOAEL of 0.1 ppm for elevated activities of several pulmonary enzymes. Hatch *et al*. (1986) and Currie *et al*. (1987a) noted 4-hour rat NOAELs of 0.1 ppm and 0.125 ppm, respectively, for increased lavage fluid protein. Illing and associates (1988) observed a 4 hour mouse NOAEL of 0.1 ppm for increased phenobarbitol-induced sleeping time.

Level Protective Against Severe Adverse Effects

Exposure of 20 mice, 10 rats, 10 guinea pigs, 10 rabbits, 2 cats, and 2 goats to 0.2 ppm phosgene for 5 hours per day for 5 days resulted in no deaths and in minimal pulmonary edema in the majority of the animals (Cameron and Foss, 1941; Cameron *et al*., 1942). In a few animals (1 rat, 1 mouse, 1 rabbit, and 3 guinea pigs) massive pulmonary edema was noted. The NRC (1986) proposed an EEGL of 0.2 ppm (0.8 mg/m³) and the AIHA (1989) proposed an ERPG-2 level of 0.2 ppm. The EEGL value includes extrapolation from 5-hour data assuming an exponent (n) of 1 for the equation $C^n * t = k$ (Rinehart and Hatch, 1964). Additional uncertainty factors (to account for differences between animals and humans, for approximation of a NOAEL, and for consideration of sensitive individuals) were not included. Hatch *et al*. (1986) reported pulmonary edema in several laboratory species after 4-hour exposures to 0.2 ppm phosgene, indicating that a lower value would be required to protect the general public.

Gross *et al*. (1965) reported that the lowest exposure level of phosgene, which produced moderate pneumonitis in rats, was 0.8 ppm. We will consider this level of 0.8 ppm for 1 hour as a NOAEL for severe pneumonitis, a severe adverse effect. Applying an interspecies uncertainty factor of 10 and an intraspecies uncertainty factor of 10 results in a cumulative uncertainty factor of 100 and a level protective against severe adverse effects for 1 hour of 8 ppb (32 µg/m^3). As indicated above, this lower value is needed to provide protection for the general public.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

Rats exposed to 1.7 ppm phosgene for 2 hours had mild to severe pneumonitis 2 days following exposure (Rinehart and Hatch, 1964; Gross *et al*., 1965). Exposure of rats to 0.5 ppm for 2 hours resulted in changes in alveolar epithelium leading to decreased diffusing capacity of the lungs (Gross *et al*., 1965). The AIHA (1989) concluded that a 1-hour exposure to phosgene below 1.0 ppm (4 mg/m^3) is not life-threatening. NIOSH (1995) lists an IDLH of 2 ppm. A 30-minute LC_{50} in mice of 5.1 ppm (HSDB, 1994) suggests that levels lower than 2 ppm are required to protect the general public from life-threatening effects.

VIII. References

(AIHA) American Industrial Hygiene Association. Emergency planning guidelines for phosgene. Akron (OH): AIHA; 1989.

Amoore JE, Hautala E. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983;3(6):272-289.

Arena JM, Drew RH, editors. Poisoning: toxicology, symptoms, treatments. Springfield (IL): CC Thomas; 1974. p. 323.

Burleson GR, Keyes LL. Natural killer cell activity in Fischer-344 rat lungs as a method to assess pulmonary immunocompetence: Immunosuppression by phosgene inhalation. Immunopharmacol Immunotoxicol 1989;11(2&3):421-443.

Cameron GR, Foss GL. Effects of low concentrations of phosgene repeated for 5 hours on 5 consecutive days in groups of different animals. Porton report No. 2316. Serial no. 63. Washington (DC): British Defense Staff, British Embassy; 1941. [cited in: NIOSH, 1976. p. 52.]

Cameron GR, Courtice FC, Foss GL. Effects of exposing different animals to low concentrations of phosgene 1:5,000,000 (0.9 mg/m^3) for 5 hours on five consecutive days. Chapter VIII in first report on phosgene poisoning. Porton report No. 2349. Washington (DC): British Defense Staff, British Embassy; 1942. [cited in: NIOSH, 1976. p. 52.]

Currie WD, Pratt PC, Frosolono MF. Response of pulmonary energy metabolism to phosgene. Toxicol Ind Health 1985;1(2):17-27.

Currie WD, Hatch GE, Frosolono MF. Pulmonary alterations in rats due to acute phosgene inhalation. Fundam Appl Toxicol. 1987a; 8(1):107-114.

Currie WD, Hatch GE, Frosolono MF. Changes in lung ATP concentration in the rat after low-level exposures to phosgene. J Biochem Toxicol 1987b;2:105-114.

Diller WF, Bruch J, Dehnen W. Pulmonary changes in the rat following low phosgene exposure. Arch Toxicol 1985;57:184-190.

Gross P, Rinehart WE, Hatch T. Chronic pneumonitis caused by phosgene. Arch Environ Health 1965;10:768-775.

Hatch GE, Slade R, Stead AG, Graham JA. Species comparison of acute inhalation toxicity of ozone and phosgene. J Toxicol Environ Health 1986;19:43-53.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM version). Denver (CO): Micromedex, Inc; 1994. (Edition expires 11/31/94).

Henderson Y, Haggard HW. Noxious gases. 2nd ed. New York: Reinhold Publishing; 1943. p. 138.

Illing JW, Mole ML, Williams TB, Menache M, Graham JA. Influence of phosgene inhalation on extrapulmonary effects in mice. Inhal Toxicol 1988;1:13-20.

Jaskot RH, Grose EC, Richards JH, Doerfler DL. Effects of inhaled phosgene on rat lung antioxidant systems. Fundam Appl Toxicol 1991;17:666-674.

Lewis DC, Alexeeff GV. Quantitative risk assessment of non-cancer health effects for acute exposure to air pollutants. Paper 89-91.4. Air and Waste Management Assoc 82nd annual meeting Anaheim (CA); 1989.

National Research Council (NRC). Criteria and methods for preparing Emergency Exposure Guidance Level (EEGL), Short-term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance Level (CEGL) documents. Vol. 2. Washington (DC): National Academy Press; 1986. p. 69-86.

NIOSH. Criteria for a recommended standard for occupational exposure to phosgene. DHEW/PHS/CDC. Pub. No. 76-137. Washington (DC): US Government Printing Office; 1976.

NIOSH. Chemical listing and documentation of revised IDLH values (as of March 1, 1995). Available at http://www.cdc.gov/niosh/intridl4.html.

Pritchard JS. Edema of the lung. Springfield (IL): CC Thomas Co; 1982. p. 180-193.

Rinehart WE, Hatch T. Concentration-time product (CT) as an expression of dose in sublethal exposures to phosgene. Ind Hyg J 1964;545-553.

Ruth J. Odor thresholds and irritation levels of several chemical substances: a review. Am Ind Hyg Assoc J 1986;47:142-151.

Winternitz MC, Lambert RA, Jackson L. The pathology of phosgene poisoning. In: Collected Studies of the Pathology of War Gas Poisoning. MC Winternitz, ed. Yale University Press. 1920.